BCMAxCD3 bispecific antibody PF-06863135: preclinical rationale for therapeutic combinations

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Abstract

BCMA-CD3 bispecific antibody PF-06863135 is currently under evaluation in an ongoing Phase 1 clinical trial in relapsed/refractory (RR) multiple myeloma (MM) patients (NCT03269136). We showed previously that BCMA-CD3 bispecific has potent single agent activity in RR MM human bone marrow aspirates in vitro and in preclinical models of human myeloma (Panowski et al, MCT 2019). Herein, we used in vitro assays, ex vivo MM patient 3D cultures, and in vivo efficacy models to study therapeutic combinations of PF-06863135 with immune checkpoint inhibitors, immunomodulatory drugs (IMiD), and gamma secretase inhibitors (GSI).

Upregulation of immune checkpoints, such as programmed cell death protein-1 (PD-1) or programmed death ligand 1 (PD-L1) has been demonstrated downstream of response to CD3 bispecifics. While PF-06863135 is effective as a single agent in ex vivo 3D primary MM cultures (EC_{50} 0.2 nM), PD-L1 was upregulated on myeloma cells. We combined PF-06863135 with anti-PD-1 in subcutaneous and orthotopic myeloma models MM.1S and MM.1S-PD-L1 in NSG mice engrafted with human T cells. PF-06863135 demonstrated single agent anti-tumor activity in the MM.1S models; however, in the MM.1S-PD-L1 model, PF-06863135 activity was blunted. When given in combination with an anti-PD-1 blocking antibody, the full thrust of the single agent anti-tumor activity of PF-06863135 was restored.

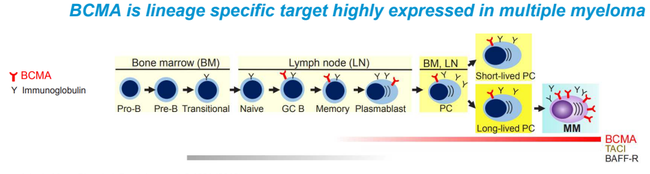
Dysfunctional, senescent like T cells may emerge downstream of T cell immunotherapies. IMiDs, such as lenalidomide, are a standard of care therapy in MM and result in immunomodulatory effects on T cells leading us to hypothesize PF-06863135 mediated tumor growth inhibition could be enhanced by combining with lenalidomide. When PF-06863135 and lenalidomide were given in combination in the human T cell engrafted established orthotopic MM.1S and MOLP8 models, an even greater anti-tumor activity was observed as compared to either agent alone. These studies suggest that PF-06863135 activity can be augmented by combinations with immunomodulatory agents such as anti-PD-1 or lenalidomide.

BCMA is shed from the surface of myeloma cells by gamma secretases, not only reducing cell surface target density but contributing to a soluble sink. When treated with GSI in vitro, myeloma cell surface BCMA expression increased concurrent with reduction in soluble/shed BCMA across a panel of myeloma and lymphoma cell lines expressing a range of BCMA. In cytotoxic T lymphocyte co-culture assays, the activity of PF-06863135 was potentiated by combining with GSI. Studies of the combination of PF-06863135 and GSI are ongoing in preclinical in vivo models of myeloma.

Taken together, our preclinical studies provide insights into mechanisms of action and resistance for PF-06863135, which has potential for profound single agent activity that can be enhanced with therapeutic combinations.

Figure 1. BCMAxCD3 (PF-06863135) is a T cell redirecting full length bispecific antibody against BCMA

BCMA is lineage specific target highly expressed in multiple myeloma



Adapted from Cho et al. Front. Immunol. 9:1821 (2018)

BCMA is a T cell redirecting bispecific antibody

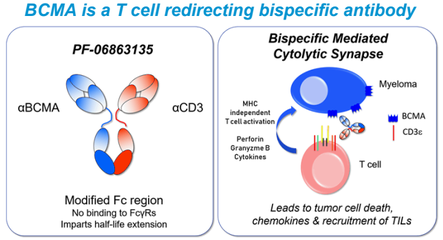
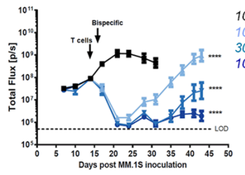


Figure 2. BCMAxCD3 is a potent & efficacious bispecific for myeloma – preclinical efficacy

MM.1S Orthotopic Myeloma Model



Molp8 Orthotopic Myeloma Model

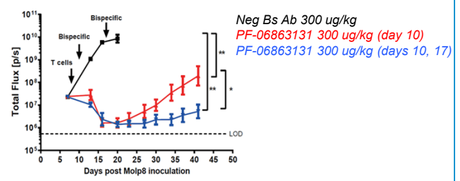
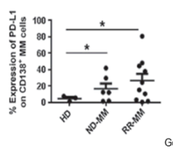
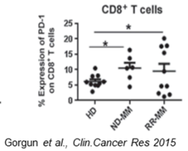


Figure 4. BCMAxCD3 activity is enhanced by combination with anti-PD1 in preclinical myeloma model

PD-1 and PD-L1 are expressed in human myeloma patients and are induced after BCMAxCD3 in preclinical experiments

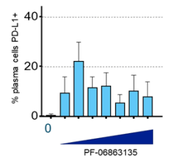
PD-L1/PD-1 are↑ in MM vs healthy donors



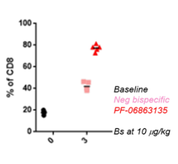


Gorgun *et al., Clin.Cancer Res 2015*

PD-L1 ↑ on PCs from MM pt 3D cultures after PF-3135



In vivo PD1 ↑ on T cells in MM.1S model



BCMAxCD3 is more effective in combination with anti-PD-1 in preclinical efficacy MM.1S-PDL1 orthotopic in vivo model

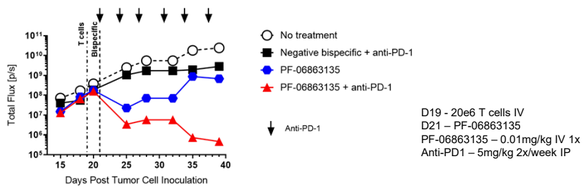
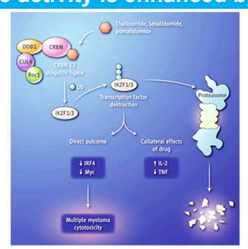


Figure 5. BCMAxCD3 activity is enhanced by combination with lenalidomide

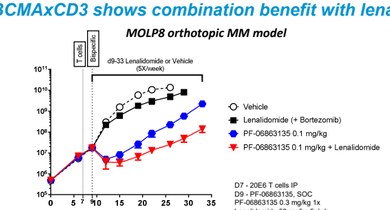


Anti-MM effects
Anti-niche effects
Increases in IL2, iNK/NKT profileration, DC maturation – orthogonal to CD3 BsAbs

Stewart et al. Science 343:256 (2014)

BCMAxCD3 shows combination benefit with lenalidomide in lenalidomide-resistant MM models

MOLP8 orthotopic MM model



MM.1S orthotopic MM model

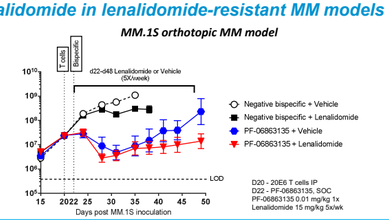
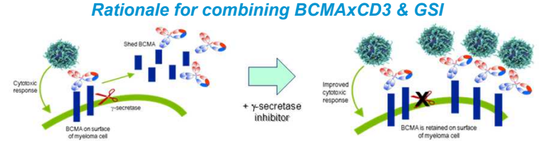


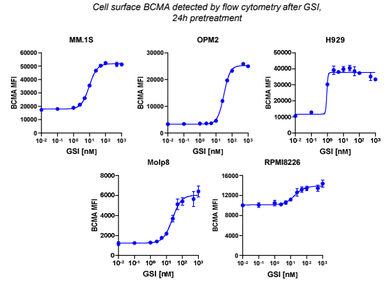
Figure 6. Combinations with gamma secretase inhibitors may improve efficacy by reducing soluble BCMA & retaining BCMA on the cell surface

Rationale for combining BCMAxCD3 & GSI

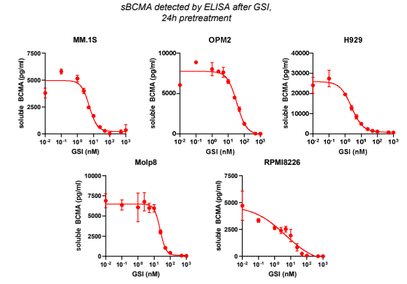


GSI increases BCMA on the surface of myeloma cells and reduces accumulation of sBCMA

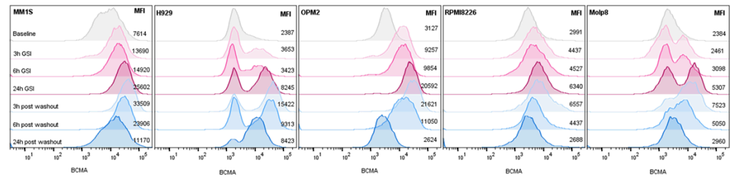
Cell surface BCMA detected by flow cytometry after GSI, 24h pretreatment



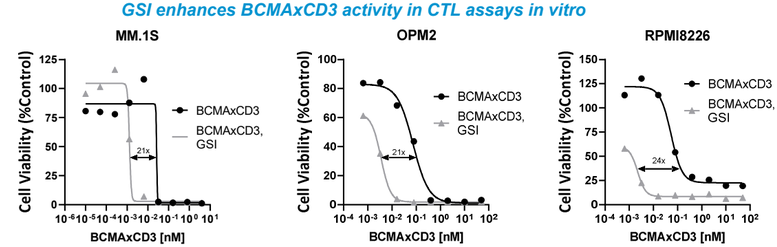
sBCMA detected by ELISA after GSI, 24h pretreatment



Cell surface BCMA detected by flow cytometry during GSI treatment and post GSI wash-out



GSI enhances BCMAxCD3 activity in CTL assays in vitro



Conclusions

- We developed a potent BCMAxCD3 bispecific for the treatment of myeloma, including relapsed/refractory disease, and is promising in pre-clinical models
- In preclinical studies, the anti-tumor efficacy of BCMAxCD3 at suboptimal doses is improved when combined with checkpoint inhibitors, IMiDs and GSI, supporting clinical rationale for dose expansion
- Next-wave of BCMAxCD3 combinations may include GSI supported by preclinical evidence that BCMA is maintained on the myeloma cell surface

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